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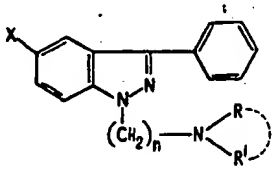
(19)

(54) INDAZOLE DERIVATIVES

(71) We, CHUGAI SEIYAKU KABUSHIKI KAISHA, a Japanese body corporate of No. 5—1, 5-chome, Ukima, Kita-ku, Tokyo, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to indazole derivatives.

The invention provides indazole derivatives having the formula:

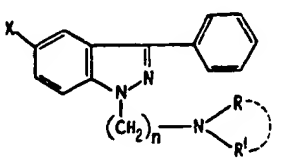


(I)

wherein X is a hydrogen atom, a halogen atom or lower alkyl group; each of R and R′ is a hydrogen atom, a lower alkyl group or a lower alkenyl group, or R and R′, together with the nitrogen atom to which they are attached, form an unsubstituted or substituted heterocyclic ring; and *n* is 1, 2 or 3.

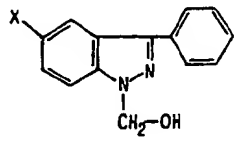
The indazole derivatives of the formula (I) are novel compounds having tranquilizing activity, antidepressive activity, anti-inflammatory activity, circulatory activity, etc., and are useful as medicines. Thus, the invention also provides a pharmaceutical composition comprising, as active ingredient, an indazole derivative of the invention and a pharmaceutically-acceptable diluent or carrier therefor.

Examples of indazole derivatives of the invention are: (1) indazole derivatives having the formula:



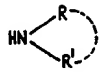
(II)

(2) indazole derivatives of formula (III) can be prepared by reacting a compound having the formula:



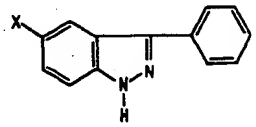
(IX)

wherein X is as defined above with respect to formula (I), with a compound having the formula:



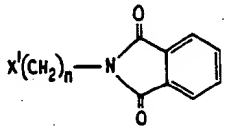
(X)

wherein R and R′ are as defined above with respect to formula (III);
(3) indazole derivatives of formula (IV) can be prepared by reacting a compound having the formula:



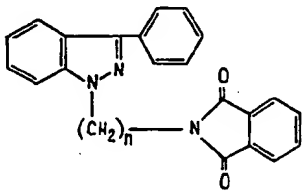
(XI)

wherein X is as defined above with respect to formula (I), with a compound having the formula:



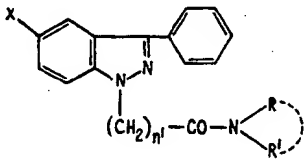
(XII)

wherein X′ is a halogen atom and *n* is as defined above with respect to formula (I);
(4) indazole derivatives of formula (V) can be prepared by reacting a compound having the formula:



(XIII)

where X and *n* are as defined above with respect to formula (I), with hydrazine;
(5) indazole derivatives of formula (VI) can be prepared by reducing a compound having the formula:



wherein *n′* is *n*-1, n being as defined above with respect to formula (VI), X is as defined above with respect to formula (I), and R and R′ are as defined above with respect to formula (VI).

In the formulae (I), (II), (III), (VI), (VIII), (X) and (XIV), R and R′ may be the same or different. In formulae (I), (III) and (X), when R and R′ taken together form a substituted heterocyclic ring, the substituent may be, for example, a methyl group or a phenyl group. In formulae (II) and (VIII), when R and R′ taken together form a substituted heterocyclic ring, the substituent may be, for example, a methyl group.

As used herein, a lower alkyl group is one containing from 1 to 4 carbon atoms (e.g. a methyl group, an ethyl group or an n-butyl group), and a lower alkenyl group is one containing 2, 3 or 4 carbon atoms (e.g. an alkyl group).

(IX), the reaction can be carried out in a one-step procedure by adding formaldehyde and amine simultaneously to the compound of the formula (VII) and reacting them under similar conditions.

In the practice of the process (4), the compound of the formula (XIII) is dissolved in an organic solvent such as ethanol and reacted with an equimolar or excessive molar amount of hydrazine, preferably hydrazine hydrate. The reaction is carried out at room temperature or a temperature above it, preferably reflux point of the solvent for 1—4 hours.

Isolation of the product (I) from the reaction mixture can be carried out by pouring the reaction mixture into ice-water, extracting the mixture with an organic solvent such as benzene or chloroform, washing the extract with water, drying the extract and further concentrating it. The product (I) is generally an oil and can be converted to an inorganic acid salt thereof such as hydrochloride and sulfate or an organic acid salt such as oxalate, malonate and succinate.

The compound of the formula (I) obtained according to the invention is a novel compound and is useful as a medicine having tranquilizing activity, antidepressive activity, anti-inflammatory activity, circulatory activity, etc.

The following examples are intended only to illustrate the invention and the invention is not limited by the examples.

Experimental Example 1.

Anti-reserpine activity

ddY Strain male mice (4—5 weeks old, body weight 23—25 g) were intraperitoneally treated with 5 mg/kg of reserpine and after 3 hours the rectal temperatures were determined. Referring to the determined temperatures, the mice were divided into groups of 6 mice each to make the mean temperature of each group as much the same as possible. 4 hours after the administration of reserpine, 100 mg/kg each of the samples was orally administered to the mice. Rectal temperatures were determined 1 hour and 3 hours after the oral administration of the samples and effects of the samples on rectal temperature were calculated as a ratio with the control drug, that is, imipramine, according to the following equation to obtain the values shown in Table 1.

$$T=\frac{\text{Temperature difference between groups treated with samples and a control group (treated with vehicle)}}{\text{Temperature difference between a group treated with imipramine and a control group (treated with vehicle)}}$$

TABLE 1.

Samples	Anti-reserpine activity
Compound of Example 3	0.7
Compound of Example 7	1.0
Compound of Example 8	0.7
Compound of Example 9	0.7
Compound of Example 10	1.0
Compound of Example 16	0.5
Compound of Example 29	1.0
imipramine	1.0
desipramine	1.0

Experimental Example 2.

Barbiturate potentiation

ddY Strain male mice (4—5 weeks old, body weight 23—28 g) in groups of 5 mice each were orally treated with 100 mg/kg of samples and 30 minutes after the

TABLE 3

Sample \ Animal	LD_{50} (mg/kg p.o.) mouse	rat	Subacute toxicity rat
Compound of Example 10	♂ 580 ♀ 660	3000~5000	not fatal at a dose of 100 mg/kg; no abnormal symptom at this dose.
Imipramine	350	900	not fatal at a dose of 50 mg/kg; At this dose normal increase in body weight is depressed and hemoglobin and blood urine nitrogen are reduced. Marginal part of liver appears dull.

Example 1.

Dimethylaminoethyl chloride hydrochloride (4.32 g) was dissolved in water (20 ml) and the solution was alkalized by the addition of aqueous sodium hydroxide solution. Then the solution was thoroughly mixed with toluene (30 ml) and the organic layer was dried over sodium sulfate. Separately, 3-phenylindazole (3.88 g) was dissolved in dimethyl formamide (60 ml) and sodium hydride, 50% pure, (1.15 g) was added to the solution, followed by adding dropwise the previously prepared toluene solution. The mixture was heated to 70°C and stirred for 75 min. at that temperature and then poured into ice-water and extracted with chloroform. The extract was washed with water, dried over sodium sulfate and concentrated by evaporation. The residue was treated with ether-hydrochloric acid to form hydrochloride. The product was recrystallized from ethanol-ether to obtain 2.0 g of 1-dimethylaminoethyl-3-phenylindazole hydrochloride (m.p. 163—165°C).

Analysis:

Calcd. for $C_{17}H_{20}N_3Cl$: C, 67.65; H, 6.68; N, 13.92 (%)
Found: C, 67.36; H, 6.59; N, 13.72 (%)

Example 2.

By the procedure similar to that described in Example 1, 3-phenyl-5-chloroindazole (4.57 g) and dimethylaminoethyl chloride hydrochloride (4.32 g) were treated to obtain 3.5 g of 1-dimethylaminoethyl-3-phenyl-5-chloroindazole hydrochloride (m.p. 200—201°C).

Analysis:

Calcd. for $C_{17}H_{19}N_3Cl$: C, 60.72; H, 5.70; N, 12.49 (%)
Found: C, 60.99; H, 5.74; N, 12.53 (%)

Example 3.

By the procedure similar to that described in Example 1, 3-phenyl-5-methylindazole (4.17 g) and dimethylaminoethyl chloride hydrochloride (4.32 g) were treated to obtain 4.0 g of 1-dimethylaminoethyl-3-phenyl-5-methylindazole hydrochloride (m.p. 191—192°C).

Analysis:

Calcd. for $C_{18}H_{22}N_3Cl$: C, 68.45; H, 7.02; N, 13.30 (%)
Found: C, 68.42; H, 7.17; N, 13.28 (%)

Example 4.

By the procedure similar to that described in Example 1, 3-phenyl-5-chloroindazole (4.57 g) and diethylaminoethyl chloride hydrochloride (5.16 g) were treated to obtain 5.1 g of 1-diethylaminoethyl-3-phenyl-5-chloroindazole hydrochloride (m.p. 185—186°C).

Analysis:

Calcd. for $C_{19}H_{23}N_3Cl_2$: C, 62.64; H, 6.36; N, 11.54(%)
Found: C, 62.41; H, 6.23; N, 11.33 (%)

Example 11.

By the procedure similar to that described in Example 1, 3-phenylindazole (3.88 g) and piperidinopropyl chloride hydrochloride (5.94 g) were treated to obtain 5.3 g of 1-piperidinopropyl-3-phenylindazole hydrochloride (m.p. 201—202°C).

Analysis:

Calcd. for $C_{21}H_{26}N_3Cl$:	C, 70.87;	H, 7.36;	N, 11.81 (%)
Found:	C, 71.11;	H, 7.39;	N, 11.89 (%)

Example 12.

By the procedure similar to that described in Example 1, 3-phenyl-5-methylindazole (4.17 g) and piperidinopropyl chloride hydrochloride were treated to obtain 5.0 g of 1-piperidinopropyl-3-phenyl-5-methylindazole hydrochloride (m.p. 222—223°C).

Analysis:

Calcd. for $C_{22}H_{28}N_3Cl$:	C, 71.43;	H, 7.63;	N, 11.36 (%)
Found:	C, 71.50;	H, 7.61;	N, 11.47 (%)

Example 13.

3-Phenyl-5-methylindazole (4.17 g) was dissolved in dimethylformamide (70 ml) and sodium hydride 50% pure (1.15 g) was added to the solution, followed by stirring it at room temperature for 10 min. To the resulting solution was added dropwise a solution of diethylaminopropyl chloride (3.59 g) in 30 ml of toluene. The mixture was stirred at 70°C for 1 hour and poured into ice-water, and extracted with chloroform. The extract was washed with water, dried over sodium sulfate and concentrated by evaporation. The residue was treated with ether-hydrochloric acid to obtain 4.5 g of 1-diethylaminopropyl-3-phenyl-5-methylindazole hydrochloride (m.p. 127—129°C).

Analysis:

Calcd. for $C_{21}H_{28}N_3Cl$:	C, 70.47;	H, 7.89;	N, 11.74 (%)
Found:	C, 70.24;	H, 8.26;	N, 11.28 (%)

Example 14.

By the procedure similar to that described in Example 13, 3-phenyl-5-chloroindazole (4.57 g) and morpholinoethyl chloride (3.59 g) were treated to obtain 3.7 g of 1-morpholinoethyl-3-phenyl-5-chloroindazole hydrochloride (m.p. 226—229°C).

Analysis:

Calcd. for $C_{19}H_{21}N_3OCl_2$:	C, 60.32;	H, 5.60;	N, 11.11 (%)
Found:	C, 60.55;	H, 5.59;	N, 11.22 (%)

Example 15.

By the procedure similar to that described in Example 13, 3-phenyl-5-methylindazole (4.17 g) and 1-morpholinopropyl chloride (3.93 g) were treated to obtain 4.1 g of 1-morpholinopropyl-3-phenyl-5-methylindazole hydrochloride (m.p. 180—182°C).

Analysis:

Calcd. for $C_{21}H_{26}N_3OCl$:	C, 67.82;	H, 7.05;	N, 11.30 (%)
Found:	C, 67.89;	H, 6.85;	N, 11.36 (%)

Example 16.

By the procedure similar to that described in Example 13, 3-phenylindazole (3.88 g) and N-methylpiperazinopropyl chloride (4.24 g) were treated to obtain 6.8 g of 1-N-methylpiperazinopropyl-3-phenyl indazole hydrochloride (m.p. 222—224°C).

Analysis:

Calcd. for $C_{21}H_{28}N_4Cl_2.H_2O$:	C, 59.29;	H, 7.11;	N, 13.17 (%)
Found:	C, 59.54;	H, 7.02;	N, 13.23 (%)

Example 17.

By the procedure similar to that described in Example 13, 3-phenyl-5-methylindazole (4.17 g) and N-methylpiperazinopropyl chloride (4.24 g) were treated to obtain 4.0 g of 1 - N - methylpiperazinopropyl - 3 - phenyl - 5 - methylindazole hydrochloride (m.p. 226—228°C).

hydroxymethyl-3-phenylindazole having a melting point between 103—105°C after recrystallization from ligroine.

Analsysis:

Calcd. for $C_{14}H_{12}N_2O$:	C, 74.98;	N, 5.39;	N, 12.49 (%)
Found:	C, 74.92;	H, 5.18;	N, 12.61 (%)

1-Hydroxymethyl-3-phenylindazole obtained above and N-phenylpiperazine were treated by a procedure similar to that described in (a) of Example 19 to obtain the same product as produced in (a) of Example 22.

Example 22.

(a) By the procedure similar to that described in Example 19, 3-phenyl-5-methylindazole (2.08 g), paraformaldehyde (0.35 g) and 2-(4'-chlorophenyl)-1,2,3,6-tetrahydro-4-methylpyridine (4.0 g) were treated to obtain 2.8 g of 1-[2'-(4''-chlorophenyl) - 1',2',3',6' - tetrahydro - 4' - methyl] - pyridinomethyl - 3 - phenyl - 5-methyl-indazole (m.p. 130—131°C).

Analysis:

Calcd. for $C_{27}H_{26}N_3Cl$:	C, 75.77;	H, 6.12;	N, 9.82 (%)
Found:	C, 76.19;	H, 6.13;	N, 10.28 (%)

(b) By the procedure similar to that described in Example 19, 3-phenyl-5-methylindazole (13.7 g) and paraformaldehyde (2.4 g) were treated to obtain 13.1 g of 1-hydroxy-3-phenyl-5-methylindazole (m.p. 109—111°C).

Analysis:

Calcd. for $C_{15}H_{14}N_2O$:	C, 75.61;	H, 5.92;	N, 11.76 (%)
Found:	C, 75.54;	H, 5.82;	N, 11.76 (%)

1-Hydroxymethyl-3-phenyl-5-methylindazole obtained above and 2-(4'-chlorophenyl)-1,2,3,6-tetrahydro-4-methylpyridine were treated by a procedure similar to that described in (a) of Example 19 to obtain the same product as produced in (a) of Example 22.

Example 23.

1-Hydroxymethyl-3-phenylindazole (2 g), morpholine (0.84 g) and 5% aqueous sodium hydroxide solution (1 ml) were dissolved in ethanol (30 ml), and the mixture was heated under reflux for 3 hours. After completion of the reaction, the mixture was concentrated under reduced pressure. The resulting oily residue was treated with ether-hydrochloric acid to obtain 1-morpholinomethyl-3-phenylindazole having a melting point between 166—167°C (decomposition) after recrystallization from ethanol-ether.

Analysis:

Calcd. for $C_{18}H_{20}N_3OCl$:	C, 65.55;	H, 6.11;	N, 12.74 (%)
Found:	C, 65.48;	H, 6.26;	N, 12.58 (%)

Example 24.

3-Phenyl-5-methylindazole (4.17 g) was dissolved in dimethylformamide (70 ml) and to the solution was added sodium hydride 50% pure (0.96 g) followed by stirring at room temperature for 10 minutes. To the resulting mixture was added a solution of phthalimidopropyl chloride (4.47 g) in dimethylformamide (50 ml) followed by stirring at 95°C for 6 hours. The reaction mixture was poured into ice-water and then extracted with chloroform. The extract was washed with water, dried over sodium sulfate and concentrated under reduced pressure to obtain 4.9 g of 1-phthalimidopropyl-3-phenyl-5-methylindazole having a melting point between 131—132°C after recrystallization from methanol.

Analysis:

Calcd. for $C_{25}H_{21}N_3O_2$:	C, 75.93;	H, 5.35;	N, 10.63 (%)
Found:	C, 75.96;	H, 5.27;	N, 10.61 (%)

Example 25.

By the procedure similar to that described in Example 24, 3-phenyl-5-chloroindazole (9.2 g), sodium hydride 50% pure (2.3 g) and phthalimidopropyl chloride (9.0 g) were treated to obtain 10.4 g of 1-phthalimidopropyl-3-phenyl-5-chloroindazole. Recrystallization from methanol gave a product having a melting point between 121—122°C.

carbamoylethyl-3-phenyl-5-methylindazole (m.p. 99—100°C) (5.0 g) was treated with the use of lithium aluminum hydride (1.5 g) to obtain 1.9 g of 1-N,N-dimethylaminopropyl-3-phenyl-5-methyl-indazole oxalate having a melting point between 184—185°C after recrystallization from ethanol.

Analysis:
Calcd. for $C_{21}H_{23}N_3O_4$: C, 65.78; H, 6.57; N, 10.96 (%)
Found: C, 65.70; H, 6.61; N, 10.82 (%)

Example 32.

By the procedure similar to that described in Example 27, 1-carbamoylethyl-3-phenyl-5-chloroindazole (m.p. 156—157°C) (5.0 g) was treated with the use of lithium aluminum hydride (1.5 g) to obtain 2.0 g of 1-aminopropyl-3-phenyl-5-chloroindazole hydrochloride having a melting point between 163—164°C after recrystallization from ethanol-ether.

Analysis:
Calcd. for $C_{16}H_{17}N_3Cl_2$: C, 59.64; H, 5.32; N, 13.04 (%)
Found: C, 59.65; H, 5.42; N, 13.20 (%)

Example 33.

1-Phthalimidopropyl-3-phenyl-5-chloroindazole (8.3 g) and hydrazine hydrate (2.0 g) were added to ethanol (150 ml) followed by heating under reflux for 3 hours. The reaction mixture was concentrated under reduced pressure and to the residue were added benzene (150 ml) and 10% aqueous sodium hydroxide solution (200 ml) followed by stirring at room temperature for 1 hour. The organic layer was separated from the mixture and it was washed with water, dried over sodium sulfate and concentrated under reduced pressure to obtain 5.5 g of 1-aminopropyl-3-phenyl-5-chloroindazole as an oily product. The product was treated with ether-hydrochloric acid to form its hydrochloride. After recrystallization from ethanol-ether, the product had a melting point between 163—164°C.

Analysis:
Calcd. for $C_{16}H_{17}N_3Cl_2$: C, 59.64; H, 5.32; N, 13.04 (%)
Found: C, 59.75; H, 5.28; N, 13.19 (%)

Example 34.

By the procedure similar to that described in Example 33, 1-phthalimidopropyl-3-phenyl-5-methylindazole (5.0 g) and hydrazine hydrate (1.5 g) were treated to obtain 3.1 g of 1-aminopropyl-3-phenyl-5-methylindazole as an oily product. The product was converted by a conventional way to its hydrochloride having a melting point between 161—163°C.

Analysis:
Calcd. for $C_{17}H_{20}N_3Cl$: C, 67.65; H, 6.68; N, 13.92 (%)
Found: C, 67.64; H, 6.76; N, 13.63 (%)

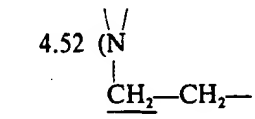
Example 35.

By the procedure similar to that described in Example 33, 1-phthalimidopropyl-3-phenylindazole (6.0 g) and hydrazine hydrate (2.0 g) were treated to obtain 3.8 g of 1-aminopropyl-3-phenylindazole as an oily product.

Infrared Absorption Spectra: (neat) (cm^{-1})

3370, 3050, 2930, 2870,
1615, 1605, 1495, 1150,
778, 750, 695

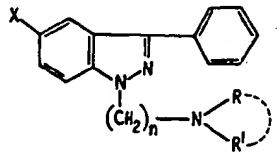
NMR: $\delta(CDCl_3)$
1.57 ($-NH_2$, 2H)
2.06 ($-C-CH_2-C-$, 2H, quintet)
2.73 ($-\underline{CH_2}NH_2$, 2H, triplet)



7.0—8.1 (aromatic proton, 9H)

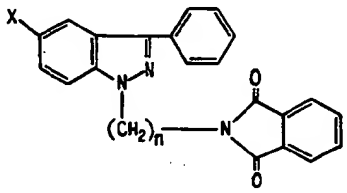
wherein X is a hydrogen atom, a halogen atom or a lower alkyl group; each of R and R′ is a lower alkyl group or an allyl group, or R and R′, together with the nitrogen atom to which they are attached, form a heterocyclic ring optionally substituted by a lower alkyl group; and *n* is 2 or 3.

3. An indazole derivative having the formula:



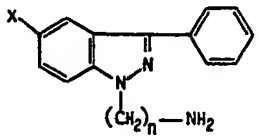
wherein X is a hydrogen atom, a halogen atom or a lower alkyl group; each of R and R′ is a lower alkyl group, or R and R′, together with the nitrogen atom to which they are attached, form an unsubstituted or substituted heterocyclic ring.

4. An indazole derivative having the formula:



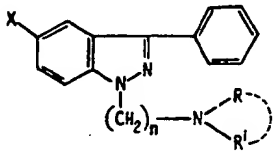
wherein X is a hydrogen atom, a halogen atom or a lower alkyl group; and *n* is 1, 2 or 3.

5. An indazole derivative having the formula:



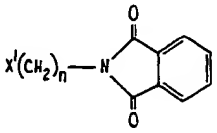
wherein X is a hydrogen atom, a halogen atom or a lower alkyl group; and *n* is 1, 2 or 3.

6. An indazole derivative having the formula:



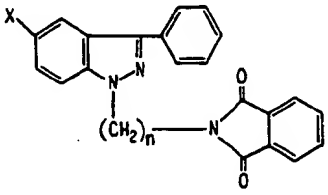
wherein X is a hydrogen atom, a halogen atom or a lower alkyl group; each of R and R′ is a hydrogen atom or a lower alkyl group, or R and R, together with the nitrogen atom to which they are attached, form a heterocyclic ring optionally substituted by a phenyl group; and *n* is 2 or 3.

7. 1-Dimethylaminoethyl-3-phenylindazole.
8. 1-Dimethylaminoethyl-3-phenyl-5-chloroindazole.
9. 1-Dimethylaminoethyl-3-phenyl-5-methylindazole.
10. 1-Diethylaminoethyl-3-phenyl-5-chloroindazole.
11. 1-Diethylaminoethyl-3-phenyl-5-methylindazole.
12. 1-Diethylaminoethyl-3-phenylindazole.
13. 1-Dimethylaminopropyl-3-phenylindazole.
14. 1-Dimethylaminopropyl-3-phenyl-5-chloroindazole.
15. 1-Dimethylaminopropyl-3-phenyl-5-bromoindazole.
16. 1-Dimethylaminopropyl-3-phenyl-5-methylindazole.
17. 1-Piperidinopropyl-3-phenylindazole.
18. 1-Piperidinopropyl-3-phenyl-5-methylindazole.
19. 1-Dimethylaminopropyl-3-phenyl-5-methylindazole.
20. 1-Morpholinoethyl-3-phenyl-5-chloroindazole.
21. 1-Morpholinopropyl-3-phenyl-5-methylindazole.



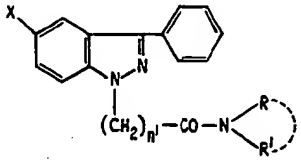
wherein X' is a halogen atom and *n* is as defined in claim 4.

47. A process for preparing an indazole derivative as claimed in claim 5, which comprises reacting a compound having the formula:



wherein X and *n* are as defined in claim 5, with hydrazine.

48. A process for preparing an indazole derivative as claimed in claim 6, which comprises reducing a compound having the formula:



wherein *n'* is *n*-1, *n* being as defined in claim 6, and X, R and R' are as defined in claim 6.

49. A process for preparing an indazole derivative as claimed in claim 1, substantially as hereinbefore described.

50. A process for preparing an indazole derivative as claimed in claim 1, substantially as described in any of the foregoing Examples.

51. An indazole derivative whenever prepared by a process as claimed in any of claims 44 to 50.

52. A pharmaceutical composition comprising, as active ingredient, an indazole derivative as claimed in any of claims 1 to 43 and 51, and a pharmaceutically-acceptable diluent or carrier therefor.

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